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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,969	02/22/2002	Cheng Cheng	4-31704A/GTI	4496

7590 04/20/2005

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,969	CHENG ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13,14,16-45,47-51,58,59,62-64 and 67-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,14,16-45,47-51,58,59,62-64 and 67-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 2/2/05. Claims 12, 15, 46, 52-57, 60-61 and 65-66 have been cancelled. Claim 41 has been amended. Claims 1-11, 13-14, 16-45, 47-51, 58-59, 62-64 and 67-83 are pending in the instant application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are new grounds of rejection herein that were not necessitated by applicants' amendment and therefore, this action is not final.

Claim Objections

Claims 23, 24, 26, 33, 35, 37 and 59 objected to because of the following informalities: the claims have abbreviations for which the common name is not readily known and therefore, should be spelled out. Claim 23 recites flt3. Claim 24 recites MIP, CCR, B7 and TAPs. Claim 26 recites MART, pmel, MAGE, GAGE, BAGE, NY-ESO, MUM, KIA, HLA-A2R1701, G-250, MUC and LDLR-FUT. Claim 33 recites TrpRS. Claim 35 recites sFlk, sNRP, sTie, IP-10, PF-4, Gro-beta, Mig, sEphB4 and Meth. Claim 37 recites CPG2, CA, CD, NR, PNP, TP and VZV-TK. Claim 59 recites RID.

Claim 23 has a period following IFNα. Claim 74 has a period preceding and following the words "alpha", "gamma" and "alpha" in line 3. Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. See Fressola v. Manbeck, 36 USPQ2d 1211 (D.D.C. 1995).

Claim 39 is grammatically incorrect for reciting that "replication is Rb-pathway defective cells is". It appears that the claim should recite that "replication in Rb-pathway".

In claim 48, "vector" is misspelled as "vecto". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-14, 16-45, 47-51, 58-59, 62-64 and 67-83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11, 13-14, 16-45, 47-51, 58-59, 62-64 and 67-83 are vague and indefinite in that the metes and bounds of "in sequential order" are unclear. It is unclear if the recited components must be in the exact recited sequence or if any order so long as it is sequential is permitted. A reading of the specification would suggest that the viral vector is comprised of the recited components in the order that is recited. However, during prosecution, claims must be interpreted as broadly as their terms reasonably allow. In the broadest reasonable interpretation, a viral vector comprising "in sequential order" can be understood to mean that the vector comprises the recited components in any sequential order so long as they are in a sequential order.

Claim 7 is vague and indefinite in that the metes and bounds of "further comprising" are unclear. Claim 7 depends from claim 6, which comprises a deletion upstream from the termination signal sequence and "further" comprises a deletion encompassing nucleotides 103

and 551. From a reading of the specification, it appears that the deletion recited in claim 7 is intended to further limit the deletion recited in claim 6. However, claim 7 recites that the vector "further" comprises a deletion suggesting that this is a second deletion. Therefore, it is unclear if the vector comprises two deletions or one. **This is a new rejection.**

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-6, 8, 9, 14, 16, 18-25, 29, 35-38, 48, 58, 59, 62, 67, 69-76, 78, 82 and 83 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al (US 2004/0151696; see entire document).

The rejection of the instant claims under 35 USC 102(e) is based upon a reading of the claims using the broadest reasonable interpretation as described above in the 35 USC 112, second paragraph rejection. Thus, a viral vector comprising "in sequential order" can mean that the vector comprises the recited components in any sequential order so long as they are in a sequential order.

Johnson et al teach an oncolytic vectors and particles that comprises a left ITR, termination signals such as those associated with the E1A or E2 genes or inserted transgenes, a human E2F-1 promoter driving expression of E1a or E4 gene and a right ITR and a packaging

signal (see e.g. figure 4, example 1 and paragraph 60). The sequential order of these components can be as detailed in figure 4. Furthermore, the vector is based upon Ad5 (see e.g. paragraph 94 or 96). The E2F-1 promoter can be considered to be tissue specific as it is specific for Rb defective cancer cells thus in the case that E2F is linked to E1A, the E2F promoter driving expression of E4 is a tissue specific promoter (see e.g. paragraph 32). Thus the vector is designed to replicate in Rb defective cells but not in normal cells (see e.g. paragraph 88). The CR region can be deleted from the E1A gene, which deletes sequences upstream of the termination signal (see e.g. paragraph 88-91). According to the examples, the E3 19k gene is deleted and the cytosine deaminase is inserted into the vector (see e.g. example 7). Otherwise the E3 gene is present (paragraph 110 and figure 4b). However, the gene can be inserted into the E1B region, which would under most conditions inactivate the E1B region (see e.g. paragraph 0101). The vector further comprises a coding sequence such as for cytokines such as TNFα or IFNγ (an immunomodulatory protein as well as antigenic protein), MIP3, cell suicide or apoptosis inducing proteins such as thymidine kinase, which can be inserted into the E3 19K or 14.7 K region (see e.g. paragraphs 101). Furthermore, tumor associated antigens or polypeptides that bind to receptors present on the tumor cell are contemplated (see e.g. paragraph 101).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following rejections of the instant claims under 35 USC 103(a) is based upon a reading of the claims using the broadest reasonable interpretation as described above in the 35 USC 112, second paragraph rejection. Thus, a viral vector comprising "in sequential order" comprises the recited components only in the recited order.

Claims 1-9, 14, 16, 18-25, 29, 35-38, 40, 41, 43, 48, 58, 59, 62, 63, 64, 67, 69-76, 78, 82 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al (US 2004/0151696; see entire document) in view of George and Blazing (5,880,102; see entire document) as evidenced by Hearing and Shenk (Cell, 1983, pages 695-703; see entire document). **This is a new rejection.**

Applicants claim a recombinant viral vector comprising in sequential order a left ITR, a termination signal, an E2F responsive promoter operably linked to a gene required for replication, a packaging signal and a right ITR.

Johnson et al teach an oncolytic vector that comprises in the following order, a left ITR, termination signals such as those associated with the E1A or E2 genes or inserted transgenes, a human E2F-1 promoter driving expression of E4 gene (or alternatively or at the same time driving expression of E1A) and a right ITR (see e.g. figure 4, example 1 and paragraph 60). The right ITR is retained to provide the regulatory elements required for viral DNA replication (see e.g. paragraph 0085). Furthermore, the vector is based upon Ad5 (see e.g. paragraph 94 or 96). The E2F-1 promoter can be considered to be tissue specific as it is specific for Rb defective cancer cells thus in the case that E2F is linked to E1A, the E2F promoter driving expression of E4 is a tissue specific promoter (see e.g. paragraph 32). Thus the vector is designed to replicate in Rb defective cells but not in normal cells (see e.g. paragraph 88). The CR region can be

deleted from the E1A gene, which deletes sequences upstream of the termination signal (see e.g. paragraph 88-91). According to the examples, the E3 19k gene is deleted and the cytosine deaminase is inserted into the vector (see e.g. example 7). Otherwise the E3 gene is present (paragraph 110 and figure 4b). However, the gene can be inserted into the E1B region, which would under most conditions inactivate the E1B region (see e.g. paragraph 0101). The vector further comprises a coding sequence such as for cytokines such as TNFα or IFNγ (an immunomodulatory protein as well as antigenic protein), MIP3, cell suicide or apoptosis inducing proteins such as thymidine kinase, which can be inserted into the E3 19K or 14.7 K region (see e.g. paragraphs 101). Furthermore, tumor associated antigens or polypeptides that bind to receptors present on the tumor cell are contemplated (see e.g. paragraph 101). The adenovirus can be altered for selective delivery to neoplastic cells based upon a cell surface protein, which binds an immunoglobin or immunoliposomes (see e.g. paragraph 0106).

Johnson et al do not teach either that the termination signal is a SV40 polyadenylation sequence or that this sequence is positioned 5' to the E1a gene or that the packaging signal is positioned 3' of the gene required for replication and prior to the right ITR.

George and Blazing teach generation of an adenovirus vector, i.e. Ad:Pac-Bgal in which a SV40 polyadenylation sequence is 3' to the left ITR and 5' of E1A gene (see e.g. figure 47). Placement of the SV40 polyadenylation sequences functions to terminate expression of sequences that are 3' to the left ITR. Furthermore, the e1a enhancer and packaging sequences are inserted at the 3' end of the vector (see e.g. figure 47 and col 2, line 6-10). In this manner, the E1A enhancer regions, which are intertwined with the packaging signal are non-operative as evidenced by Hearing and Shenk while the packaging functions are retained (see e.g. abstract).

Therefore, in the vector of George and Blazing expression of E1A or gene substituted for E1A can be expressed by for example tissue-specific promoters without read through from the E1A enhancer. The results of these manipulations are deletion of the region of Ad5 that comprises nucleotides 103-551.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to move the packaging signal in the vector taught by Johnson et al to the 3' end of the vector as taught by George and Blazing as evidenced by Hearing and Shenk because Johnson et al teach that it is within the ordinary skill of the art to generate recombinant virus in which the E4 gene is under control of the E2F promoter and because George and Blazing teach that it is within the ordinary skill of the art to move the packaging signal to the 3' end of the adenovirus. One would have been motivated to do so in order to receive the expected benefit of reducing E1A in the cell such that the virus is E1a-RB replication deficient as described by Johnson et al (see e.g. paragraph 0089). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 49-51 and 79-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al (US 2004/0151696; see entire document) in view of George and Blazing (5,880,102; see entire document) as evidenced by Hearing and Shenk (Cell, 1983, pages 695-703; see entire document) further in view of Krasnykh et al (JVI, 1998, pages 1844-1852). **This is a new rejection.**

Applicants claim a recombinant viral vector comprising in sequential order a left ITR, a termination signal, an E2F responsive promoter operably linked to a gene required for replication a packaging signal and a right ITR. Particles comprise a targeting ligand in the HI loop of the fiber protein.

The teachings of Johnson and George and Blazing and Hearing and Shenk are as above except; none teach insertion of targeting ligands into the HI loop of the fiber protein.

Krasnykh et al teach targeted vectors that are capable of gene delivery to selected cell types *in vivo* by incorporation of heterologous ligands in the HI loop of the fiber protein. The HI loop possesses several properties, which predicts its utility as a site for ligand incorporation. Specifically, the HI loop does not contribute to the intramolecular interaction in the knob such that the ligand will not affect trimerization. The HI loop is exposed outside the knob and insertions should not affect correct folding of the entire knob (see e.g. page 1845, col 1). Krasnykh et al propose insertions into the HI loop for generation of retargeted vectors that can be directed to specific cells (see e.g. page 1851, col 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to specifically insert the targeting ligands taught by Johnson et al into HI loop of the fiber protein as taught by Krasnykh et al because Johnson et al teach that it is within the ordinary skill of the art to generate recombinant virus in which a targeting ligand is used to specifically target cells and because Krasnykh et al teach that it is within the ordinary skill of the art to insert targeting ligands into the HI loop of the fiber protein. One would have been motivated to do so in order to receive the expected benefit of cell retargeting in which the ligand is exposed outside the knob and insertions should not affect correct folding of the entire knob or trimerization.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 26-28 and 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson et al (US 2004/0151696; see entire document) in view of George and Blazing (5,880,102; see entire document) as evidenced by Hearing and Shenk (Cell, 1983, pages 695-703; see entire document) further in view of Compagni et al (Cancer Research, 2000, pages 7163-7169; see entire document) or Griscelli et al (PNAS, 2000, pages 6698-6703; see entire document) or Kaplan et al (American Association of Immunologists, 1999, pages 699-707) or Ali et al (Gene Therapy, 1998, page 1561-1565). **This is a new rejection.**

Applicants claim a recombinant viral vector comprising in sequential order a left ITR, a termination signal, an E2F responsive promoter operably linked to a gene required for replication a packaging signal and a right ITR. The vector expresses tumor-associated antigens such as gp100, MART-1 or trp or anti angiogenic proteins such as angiostatin or antagonists of FGF or inhibitors of PDGF or fragments of TrpRS or antibodies that block inhibitory signals.

The teachings of Johnson and George and Blazing and Hearing and Shenk are as above except; none of the teachings teach that the vector also expresses tumor-associated antigens such as gp100, MART-1 or trp or anti angiogenic proteins such as angiostatin or antagonists of FGF or inhibitors of PDGF or fragments of TrpRS or antibodies that block inhibitory signals.

Griscelli et al teach that angiostatin is a specific inhibitor of endothelial cell proliferation. Griscelli et al express angiostatin using adenovirus to antagonize growth of endothelial cells

during the early stages of tumor angiogenesis (see e.g. page 6698, col 2, last paragraph and page 6703, col 1-2). Furthermore, in combination with cytotoxic therapies such as radiotherapy angiostatin enhances the response of larger tumors to angiostatin (see e.g. page 6698, col 2, paragraph 3).

Compagni et al teach use of soluble FGFR (sFGFR) as an antagonist of FGF function. Adenovirus expressing sFGFR were used to specifically repress proliferation and differentiation induced by FGF1 (see e.g. page 7168, col 1, paragraph 2). sFGFR was potent in inhibiting tumor growth and impairing tumor angiogenesis (see e.g. abstract and page 7168, col 2, paragraph 1).

Kaplan et al teach that dendritic cells transduced with sequences encoding several tumor associated antigens or peptides induce an Ag specific CTL response resulting in protection from tumor challenge and resulting in regression of tumors (see e.g. abstract). The cells were transduced with adenovirus expressing MAA, gp100, tyrosinase related peptide (TRP) and MART-1.

Ali et al teach expression of CTLA4-Ig from adenovirus to inhibit destruction of transduced cells (see e.g. page 1563, bridging paragraph col 1-2). Expression of CTLA4-Ig block host immune responses to the adenovirus for enhanced transgene expression by blocking the B7-CD28 interactions between antigen presenting cells and T cells to prevent the costimulatory signals required for T cell survival and proliferation (see e.g., abstract).

Otani et al teach that a fragment of human TrpRS functions as a potent antagonist of VEGF angiogenesis (see e.g. abstract).

Zhao et al teach adenovirus mediated decorin gene transfer to prevent TGF-β induced inhibition of lung morphogenesis (see e.g. abstract). Decorin was expressed using a recombinant

adenovirus, which ameliorated excessive levels of TGF-β signaling in the developing lung. Excessive TGF-b results in abnormalities of lung growth, differentiation and development (see e.g. L413, col 1, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the viral vector taught by Johnson et al in view of George and Blazing as evidenced by Hearing and Shenk to express the transgenes taught by Griscelli et al, Compagni et al, Kaplan et al, Ali et al, Otani et al and Zhao et al because Johnson et al in view of George and Blazing as evidenced by Hearing and Shenk teach that it is within the ordinary skill of the art to generate recombinant adenovirus that express heterologous genes and Griscelli et al, Compagni et al, Kaplan et al, Ali et al, Otani et al and Zhao et al teach that it is within the ordinary skill of the art to express transgenes that express products such as angiostatin, decorin, fragments of TrpRS, CTLA4-Ig MAA, gp100, tyrosinase related peptide (TRP) and MART-1 and sFGFR. One would have been motivated to do so in order to receive the expected benefit of antagonizing growth of endothelial cells during the early stages of tumor angiogenesis (see e.g. Griscelli et al) or to inhibit tumor growth and impair tumor angiogenesis (see Compagni et al and Otani et al) or for protection from tumor challenge and for regression of tumors (see e.g. Kaplan et al) or for enhanced transgene expression (see Ali et al) or to prevent TGF-β induced inhibition of lung morphogenesis (see e.g. Zhao et al) and Johnson et al teach viral vector to be used to treat cancer. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

Claims 1-11, 13-14, 16-45, 47-51, 58-59, 62-64 and 67-83 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The Central Fax number for official documents is (703)-872-9305. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

April 12, 2005

Daniel M. Sullivan
Patent Examiner
TC 1600